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09/245,198	02/05/1999	JEFFREY BROWNING	A003	4642

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EXAMINER
SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/245,198	Applicant(s) BROWNING ET AL.	
	Examiner Richard Schnizer	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10,28,30,31 and 36-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *2 and 3* is/are allowed.

6)☒ Claim(s) *1,4-8,10,28,30,31 and 36-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's amendment filed 6/6/02 was entered as Paper No. 22.

Claims 9, 11-27, 29, and 32-35 were canceled in Paper No. 19.

Claims 1-8, 10, 28, 30, and 31 remain pending and are under consideration in this Office Action.

Rejections Withdrawn

Applicant's amendments and arguments are sufficient to overcome the rejections under 35 USC 112 first paragraph.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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Claims 1, 4-8, 10, ~~28-31~~ 28, 30, 31, and 36-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New Matter

Claim 4 recites the limitation "nucleic acid encoding a polypeptide comprising a portion that is at least 50% identical with amino acids 81-284 of SEQ ID NO:4". The specification fails to provide literal support for this limitation, so it constitutes new matter. At page 7 the specification provides support for nucleic acids encoding polypeptides that have at least 50% homology with DNA encoding the C-terminal receptor binding domain of TRELL, but require that these sequences must also encode either SEQ ID NO:2 or SEQ ID NO:4. See page 7, lines 13-18. Instant claim 4 embraces a broader genus than this because it is not limited to nucleic acids encoding SEQ ID NO:2 or NO:4. The species of the genus which do not encode SEQ ID NOS:2 or 4 represent new matter.

Claim 5 requires that polypeptides encoded by the claimed polynucleotides must be capable of binding to cells to which SEQ ID NOS: 2 or 4 bind. Applicant points to page 18, lines 23-26 and pages 36 and 37 for support for the amendment. Page 18, lines 23-26 teaches that analogs of TRELL include polypeptides which differ from SEQ ID NOS: 2 or 4, but which retain "the activity" of TRELL. Pages 36 and 37 teach an assay for cytotoxicity, results of this assay, and results of an undisclosed assay for TRELL binding to cells. The specification fails to provide support for the particular combination of limitations required by the claim, because the specification fails to define which activity of TRELL must be retained. Table II on page 37 shows that binding of TRELL to cells rarely leads to cytotoxicity, thus these two activities are not synonymous. The specification provides no literal support for polypeptides that vary in sequence

from SEQ ID NOS: 2 or 4, and which retain the ability to bind to cells to which SEQ ID NOS: 2 or 4 also bind. It is noted that, prior to amendment, claim 5 required the polypeptides to have the biological activity of TRELL. As amended the polypeptides may bind to *any* receptor on a cell that also binds SEQ ID NO:2 or 4 (TRELL). This allows for a much broader range of biological activities than previously contemplated, and substantially broadens the claim.

Written Description

Claims 1, 4-8, 10, 28-31, and 36-38 embrace polynucleotides encoding polypeptides **comprising** SEQ ID NO:2. SEQ ID NO:1 encodes SEQ ID NO:2, and is a partial cDNA encoding a portion of the mouse homolog of TRELL. This is apparent because SEQ ID NO:2 corresponds to amino acids 60-284 of human TRELL (SEQ ID NO:4), and encodes only a partial transmembrane domain, and no N-terminal cytoplasmic domain. See e.g. Fig 1. All of the rejected claims embrace a full-length cDNA encoding a polypeptide comprising SEQ ID NO:2, but the specification fails to adequately describe such a molecule. The courts have found that merely describing the functional characteristics of a protein encoded by a particular nucleic acid is insufficient to adequately describe the genus of nucleic acids encoding that protein. A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. See Oka, 849 F.2d at 583, 7 USPQ2d at 1171. Conception does not occur unless one has a mental picture of the structure of the chemical, or is

able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by a principal biological property, e.g., binding to cells that bind SEQ ID NOS:2 or 4, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. When an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, conception has not been achieved until reduction to practice has occurred, i.e., until after the gene has been isolated. *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). The instant application does not provide a written description that would allow one of skill in the art to immediately envisage the specific structure for the full length mouse cDNA of TRELL. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed* (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As there disclosure of only a single species of the polynucleotides, the skilled artisan cannot envision the detailed chemical structure of the claimed genus, particularly of the full length cDNA, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of any method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a

potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

It is noted that claims 2 and 3, not included in this rejection, use the transitional phrase "consisting essentially of" rather than "comprising". Regarding this phrase MPEP 2163 states:

> "By using the term consisting essentially of,' the drafter signals that the invention necessarily includes the listed ingredients and is open to unlisted ingredients that do not materially affect the basic and novel properties of the invention. A consisting essentially of' claim occupies a middle ground between closed claims that are written in a consisting of' format and fully open claims that are drafted in a comprising' format." PPG Industries v. Guardian Industries, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998).

For this reason, claims 2 and 3 are considered to not embrace a full-length mouse cDNA, and are adequately described.

The specification also fails to describe claims 4 and 5 for the reasons given below. Claim 4 is drawn to substantially purified DNA that hybridizes to any fragment of at least 20 consecutive bases SEQ ID NOS: 1 or 3, wherein the DNA encodes a polypeptide at least 50% homologous with amino acids 81-284 of SEQ ID NO:4. Claim 5 is drawn to a substantially purified DNA that encodes the amino acid sequence of SEQ ID NO: 2 or 4, but which must encode alterations, deletions, or substitutions of these sequences that do not prevent binding of the polypeptides to cells that bind SEQ ID NOS:2 or 4. The following section of the guidelines on written description is pertinent.

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or

> by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

Claim 4 requires no more than about 36% overall amino acid identity with SEQ ID NO:4 (50% of 204, expressed as a percentage of the total protein length, 284 amino acids), and recites no limitations regarding the function of the encoded polypeptide. Thus the variation in the claimed genus is substantial. Claim 5 differs from claim 4 in that it requires a polypeptide function, but it sets forth no structural limitations, allowing unlimited substitutions, deletions, and additions so long as the resulting polypeptide binds to a cell that is bound by SEQ ID NOS:2 or 4. There is no requirement that the same receptor must be bound, and the specification discloses that the receptors for SEQ I D NOS 2 and 4 are unknown. See page 38, line 15. Clearly the variation in this genus is substantial as well. The specification fails to provide any guidance as to the relationship between the structure of the receptor binding domain and its function. In particular, there is no guidance as to how the domain can vary while still retaining its function *e.g.* no specific examples are given regarding specific substitutions that can be made while retaining any TRELL function. Because the variation in the claimed genuses is substantial, and because the function of polypeptides comprising amino acid sequence alterations is unpredictable, the disclosure of only two nucleic acid sequences does not constitute a written

description that would allow one of skill in the art to immediately envision the specific structure for any non-disclosed polynucleotide, including those with homology to the receptor binding domain, or those with TRELL activity but which vary from SEQ ID NOS: 1 and 3 by insertions deletions or alterations. As noted above, *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed* (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

As there is no disclosure of the polynucleotides, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

The limited information provided in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the broadly claimed genuses of polynucleotides at the time the application was filed. Thus it is concluded that the written description provision of 35 U.S.C. 112, first paragraph, is not satisfied for the

claimed polynucleotides. Applicants are reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Enablement

Claims 4, 5 and 28-31 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acid molecules encoding SEQ ID NOS:2 or 4, and for methods of expressing SEQ ID NOS: 2 or 4 in mammalian cell *in vitro*, does not reasonably provide enablement for nucleic acid molecules encoding variants of SEQ ID NOS:2 or 4 which do not comprise exactly the same amino acid sequences as SEQ ID NOS:2 or 4, or for methods of expressing any polypeptide in a mammalian cell *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims, for the reasons of record in Paper Nos. 11, 15, and 20.

Claims 4 and 5 are drawn to nucleic acids encoding variants of the polypeptides of SEQ ID NOS:2 and 4. SEQ ID NO:2 comprises the amino acid sequence of mouse TRELL, SEQ ID NO:4 comprises the amino acid sequence of human TRELL. Claim 4 requires that the nucleic acid must encode a polypeptide that is at least 50% homologous with amino acids 81-284 of SEQ ID NO:4. Claim 5 requires that alterations, substitutions, or deletions must be made to SEQ ID NOS: 2 or 4, but that these changes cannot abolish the biological activity of TRELL. Thus the

claims embrace nucleic acids encoding polypeptides that may vary substantially from the disclosed amino acid sequences of SEQ ID NOS:2 and 4.

The specification teaches the polynucleotides of SEQ ID NOS 1 and 3, which encode amino acid sequences of SEQ ID NOS: 2 and 4. The specification also teaches the construction of a form of human TRELL lacking the transmembrane region of TRELL, and consisting of some fraction of the extracellular TRELL domain of TRELL linked to a secretion signal and a myc epitope tag. See pages 34 and 35. However, it is unclear if this polypeptide has any TRELL biological activity. The specification discloses a functional test of TRELL activity at page 36, and results are given in Table II on page 37. The test on page 36 discloses that human TRELL was used in the assay. Thus it is unclear as to whether the modified human TRELL or the wild type human TRELL was used in the assay. Thus the specification teaches only two forms of TRELL which can be considered to be functional, SEQ ID NOS: 2 and 4.

Claim 4 specifically requires a nucleic acid encoding a polypeptide with 50% homology to a receptor binding domain of a TRELL. However, the specification fails to define the limits of any receptor binding domain of any TRELL, and it is not disclosed in the prior art of record. Thus one of skill in the art could not calculate whether or not a given polypeptide was 50% identical to a receptor binding domain of TRELL. In Genentech, Inc, v Novo Nordisk A/S, the court found that when the specification omits any specific starting material required to practice an invention, or the conditions under which a process can be carried out, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In this case, the identification of the precise limits of a TRELL receptor binding domain cannot be considered a minor detail which can be omitted in the process of providing an enabling disclosure, and one of skill in the art could not make the claimed nucleic acids, other than those encoding polypeptides comprising SEQ ID NOS:2 or 4, without undue experimentation.

Pertinent to the variant forms of TRELL encompassed by claims 4 and 5, the prior art also teaches that the effects of amino acid substitutions and deletions on protein function are highly unpredictable. Rudinger (In Peptide Hormones J.A. Parsons, Ed. University Park Press, Baltimore, 1976, page 6) teaches that "[t]he significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study." Furthermore Ngo et al (In The Protein Folding Problem and Tertiary Structure Prediction, K. Merz Jr. and S. Legrand, Eds. Birkhauser, Boston, 1994, see page 492) teaches that "[i]t is not known if there exists an efficient algorithm for predicting the structure of a given protein from its amino acid sequence alone. Decades of research have failed to produce such an algorithm". One might argue that it would not be undue

experimentation to express and assay polypeptides individually, and thereby empirically determine the function of each one. However as set forth in *In Re Fisher*, 166 USPQ 18(CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and **their performance characteristics predicted by resort to known scientific laws**; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with the degree of unpredictability of the factors involved.

Emphasis added. Taken together, the teachings of the prior art indicate that substitutions, additions and deletions of SEQ ID NOS: 2 and 4 may produce inactive proteins, and that the functions of altered versions of SEQ ID NOS: 2 and 4 are highly unpredictable. Because the effects of alterations to SEQ ID NOS:2 and 4 are unpredictable, and because the specification fails to teach which specific alterations can be made without abolishing TRELL activity, one of skill in the art could not make the claimed nucleic acids, other than those encoding polypeptides comprising SEQ ID NOS:2 or 4, without undue experimentation.

Claims 28, 30 and 31 are drawn to methods of expressing TRELL in a mammalian cell. It is readily apparent that this invention may be used in vitro for the production of the TRELL protein and for its subsequent use in studying TNF receptor signal transduction. However, the specification also teaches that the nucleic acids of the invention may be used for gene therapy for inducing antitumor responses. See e.g. page 6, line 32 to page 7, line 1; page 8, lines 9 and 10; and page 13, lines 16-22.

The specification provides very limited guidance regarding methods of gene therapy, generally disclosing that the claimed DNA sequences can be used to express TRELL under abnormal conditions. The sequences could be expressed in tumor cells under the direction of promoters appropriate for such applications and such expression could enhance anti-tumor immune responses or directly affect the survival of the tumor. In addition, the sequences can be used to affect the survival of an organ graft by altering the local immune response (see page 13 of the specification). However, the specification does not disclose abnormal conditions, other than cancer or organ graft, which can be treated by expressing a polynucleotide encoding TRELL. The specification also fails to disclose the types of tumors in a patient which could be treated by expressing a polynucleotide encoding TRELL, or any alterations in the local immune response as a function of the expression of a polynucleotide encoding TRELL. The specification does not disclose appropriate promoters to use, appropriate target sites for delivery of the polynucleotide, appropriate expression vectors required in the delivery of the polynucleotide, or the level of expression of the polynucleotide such that an anti-tumor response or an alteration in the local immune response is achieved. It is further noted that the specification discloses that only one cell line of eleven cell lines tested *in vitro* displayed any response to a TRELL peptide, and this response required the presence of interferon-gamma (see Table II on page 37 of the instant application). Clearly, the showing in the specification is not sufficient to solve the art-recognized problems associated with gene therapy, as set forth by Verma and Orkin (see Paper Nos. 11 and 15). Thus, as stated in the Paper Nos. 11 and 15, the specification is non-enabling for gene

therapy protocols as the specification does not disclose methods by which the skilled artisan could predictably and reproducibly introduce and express TRELL polynucleotides in a mammal for therapeutic effect of any disease or disorder. This portion of the rejection may be overcome by limiting claims 28-31 to methods of expressing TRELL in a mammalian cell *in vitro*.

Response to Arguments

Applicant's arguments filed 10/11/01 have been fully considered with respect to the grounds of rejection set forth above, but they are not persuasive.

Applicant's amendments overcome the portion of the rejection directed to a lack of description of genomic clones. With respect to the description of flanking sequences, the Examiner agrees that flanking sequences such as those found in expression vectors or fusion partners are conventional in the art and adequately described. However, the flanking sequences that correspond to the 5' terminus of a full length mouse TRELL cDNA are undescribed, and the written description requirement is not met for the reasons set forth above. This portion of the rejection can be overcome by limiting claims to comprising nucleic acids "consisting essentially of nucleic acids encoding SEQ ID NO:2". The existing "comprising" language is acceptable with reference to nucleic acids encoding SEQ ID NO:4 because SEQ ID NO:4 appears to be a full-length cDNA.

At page 4, second paragraph, Applicant asserts that limitation of nucleic acid claims to precise nucleotides disclosed is unduly restrictive in light of the disclosure, the knowledge of one

of skill in the art, and with the generally accepted practice in the US Patent Office. This argument is unpersuasive because it lacks support.

At page 5 of the response, Applicant argues that sufficient guidance is given to allow one of ordinary skill in the art to determine whether nucleic acid sequences encoding a protein 50% identical to the extracellular domain of SEQ ID NOS:2 or 4 also contains the biologically active component of the TRELL molecule. This argument is unpersuasive with regard to claim 4, because claim 4 recites no functional limitation and embraces a much broader genus of sequences. Applicant argues that the description of what portions of the molecule correspond to the N- C- and transmembrane domains, combined with the limitation that the C-terminal domain must be 50% identical to SEQ ID NO:4 constitutes sufficient chemical/structural information of the claimed genus to satisfy written description, when combined with functional assays to assess the function of the encoded proteins. This argument appears to be based on enablement, rather than written description. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115). The description of how to make a particular molecule does not suffice as a description of that molecule. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Applicant considers the enablement rejection at pages 6-9 of the response.

At paragraph 2 of page 6, Applicant asserts that claims 4 and 5 have been amended to require 70% identity to the extracellular domain of TRELL. This is incorrect. Claim 4 requires

only 50% identity, and claim 5 requires no identity at all. Applicant's assertion that one of skill in the art could easily determine which polypeptides embraced by the claims included the requisite function is unsupported, and in any event, claim 4 requires no polypeptide function. In claim 5 on the other hand, the recited polypeptide is not required to have any sequence identity with TRELL, and is only required to bind to a cell that binds TRELL. It is apparent to one of ordinary skill in the art that such cells will have myriad receptors binding myriad ligands. However, the specification describes only 2 ligands, SEQ ID NOS:2 and 4, and no receptor for these ligands. The only correlation between structure and the required function provided by the specification is the fact that the TRELL has a C-terminal extracellular domain that is responsible for receptor binding. There is no description of the structure/function characteristics of the receptor binding domain that could be used to identify the other members of the genus. In the paragraph bridging pages 6 and 7, Applicant appears to argue that the discovery that the N-terminal domain of TRELL is cytoplasmic, whereas the C-terminal domain is extracellular, somehow enables one to determine which amino acid substitutions, deletions, or additions will not abolish the binding activity of TRELL. Applicant indicates that this information makes it a matter of routine experimentation to express the variants of TRELL and assay them individually. Applicant's assertion that this is a "far cry" form the situation addressed in *In re Fisher* is unsupported. Applicant has failed to explain why the findings of the court in *In re Fisher* do not apply in this situation. The Office has established that the effects of amino acid substitutions on protein structure and function are highly unpredictable such that there are no known scientific

laws which one could use to accurately predict the effects of such substitutions on polypeptide function. Applicant concludes by asserting that one of skill in the could make numerous substitution and deletion mutants and test them using the disclosed assays by routine experimentation. This is true. However, the specification has not taught how to determine a priori which of the resulting polypeptides will have the desired function. In view of the vast breadth of the claim, the limitless number of substitutions that may be made, and the failure of the specification to teach the structural or functional roles of specific amino acids in the binding domain of the polypeptide, one would have to perform undue experimentation to make the invention as claimed.

At pages 8 and 9, Applicant considers the rejection of claims 28, 30, and 31. In the second paragraph on page 8, Applicant asserts that the techniques and material required to express genes in vivo are well known and available to those of ordinary skill in the art, and the specification need not disclose what is routine and well known. This is true. However the instant specification teaches no use for in vivo gene expression other than therapy. So, claims that embrace in vivo gene expression read on gene therapy. As discussed above, therapeutic gene expression in vivo is clearly not routine in the art. For this reason, the specification should provide the guidance that is missing from the prior art. In the paragraph bridging pages 8 and 9, Applicant asserts that because the specification teaches that TRELL may be used to enhance anti-tumor responses or directly affect the survival of the tumor, expression of TRELL in tumor cells is expected to have a positive effect on the existing ant-tumor response. This is unpersuasive

because, as noted above gene delivery and expression in vivo is unpredictable. Applicant has provided no guidance as to what level of expression is required for therapeutic effect, how to obtain that level, what proportion of the tumor must be transfected in order to achieve therapy. This information is not well known and not available to the public. In view of the unpredictability in the art of gene therapy, this information should be disclosed in the specification. The same arguments apply to the use of TRELL nucleic acids for promoting organ graft survival.

For these reasons the rejections are maintained.

Conclusion

K.T. 8/24

Claims 2 and 3 are allowable.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.

JAMES KETTER
PRIMARY EXAMINER